Correspondence

AIDS 2020, **34**:795–799

An HIV-infected patient with acute retinal necrosis as immune reconstitution inflammatory syndrome due to varicella-zoster virus

Acute retinal necrosis (ARN) is characterized by confluent, peripheral, necrotizing retinitis, peripheral occlusive vasculopathy, and an inflammatory reaction in the vitreous or anterior chamber [1,2]. Varicella-zoster virus (VZV) is the causative pathogen in 50–80% of ARN cases [1]. Patients with human HIV infection are a high-risk group for development of ARN [2]. Although the prognosis of HIV-infected patients has improved markedly in recent years with the advent of antiretroviral therapy (ART), immune reconstitution inflammatory syndrome (IRIS) remains as a severe complication [3]. The clinical features and prognosis of ARN during IRIS resulting from VZV in patients with HIV are unclear because no cases appear to have been reported previously. Appropriate prophylaxis for VZV-ARN associated with IRIS in HIV patients remains to be established.

A 38-year-old Japanese man was admitted to our hospital with a 10-day history of bilateral photophobia, and partial visual field loss in the right eye. He had been diagnosed with HIV infection 3 months before this admission. He had developed disseminated VZV infection with aseptic meningitis 7 weeks before admission and had been treated with acyclovir (10 mg/kg every 8 h) for 16 days following 5 days of intravenous vidarabine (10 mg/kg every day). Quantitative PCR testing of cerebrospinal fluid (CSF) samples before and after this treatment showed 1.2×10^6 and 3.6×10^2 copies/ml of VZV, respectively. No abnormal retinal findings had been found during treatment. About 5 weeks before this admission, ART with a coformulation of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate had been initiated to him. The $CD4^+$-positive lymphocyte count had been 27/μl, and quantitative PCR testing for HIV1 had shown 3.3×10^5 copies/ml before initiating ART. Funduscopic examination on admission revealed new white necrotic lesions bilaterally in the peripheral retina (Fig. 1) and vitreous opacity. Decimal best-corrected visual acuity (BCVA) on admission was 1.2 in the right eye and 1.2 in the left eye. At the time of admission, $CD4^+$-positive T-cell count was 133 cells/μl, and the HIV1-RNA viral load was 1.0×10^2 copies/ml. Treatment failure of initial meningitis was excluded for the negative result of quantitative PCR testing for VZV in the CSF taken on admission. He was diagnosed ARN as IRIS due to VZV based on the provided diagnostic criteria [4], and was treated with intravenous foscarnet at 90 mg/kg every 12 h, oral prednisolone at 1 mg/kg/day, and oral aspirin. ART was continued. On hospital day 5, qualitative PCR testing of aqueous humor revealed positive results for VZV. Intravenous acyclovir at 10 mg/kg every 8 h was administered to him in place of intravenous foscarnet. Intravitreal ganciclovir injections of 400 μg/0.1 ml were administered to the right eye on hospital days 6 and 13, and to the left eye on hospital days 8 and 20. In addition, vitrectomy combined with silicone oil injection, scleral buckling, and cataract extraction with intraocular lens implantation was performed for the right eye on hospital day 15 to prevent retinal detachment. After this combined-modality therapy, progression of retinal

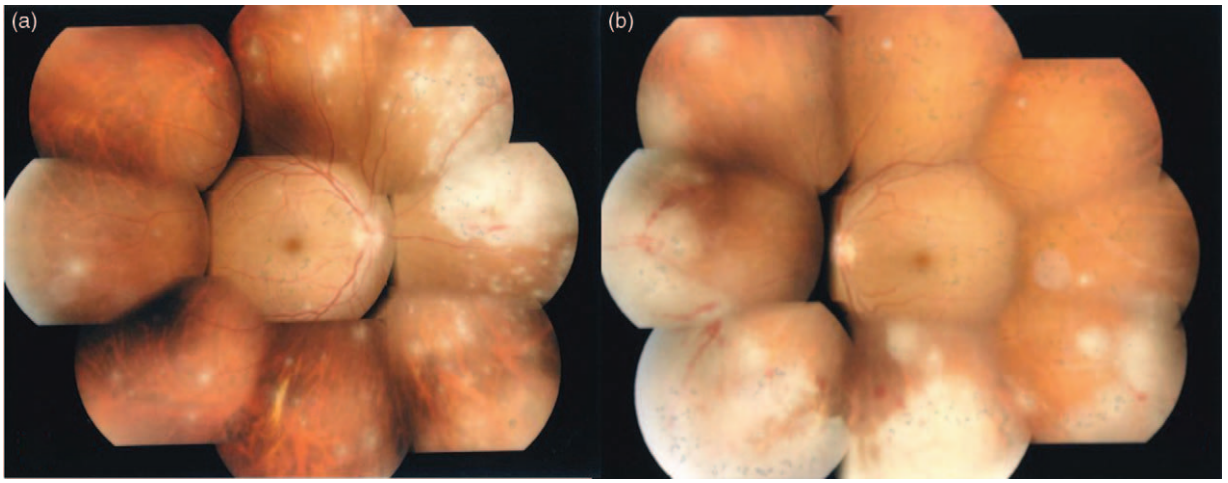

Fig. 1. Appearance of the ocular fundus on admission (a, right eye; b, left eye). White necrotic lesions are evident in the peripheral retina bilaterally.

necrosis and opacity of the vitreous body stopped. However, final decimal BCVA decreased to 0.3 in the right eye and 0.2 in the left eye, and partial visual field defects remained bilaterally. On hospital day 30, he was discharged under long-term administration of valacyclovir for secondary prophylaxis and tapering oral prednisolone. After discharge, molecular analysis of the aqueous humor on admission by PCR and sequencing revealed no mutations in the thymidine kinase genes for acyclovir resistance in the VZV [5]. IRIS due to VZV could lead to ARN in HIV patients. There were some previous case reports about central nerve system (CNS)-IRIS due to VZV [6–8]. Two cases developed cerebral vasculitis due to VZV-IRIS following 2–3 weeks of treatment with intravenous acyclovir for CNS infection [6,7]. Another case report of the myelitis due to VZV indicated that CNS-IRIS was induced by an immune response to pathogens localized to the spinal cord [8]. We consider that a small amount of pathogen remaining in the CSF could induce IRIS in these cases, despite adequate treatment. Secondary prophylaxis with antiviral drugs against VZV in HIV patients has not been recommended in recent guidelines [9]. However, other opportunistic infections of the CNS, such as cytomegalovirus encephalitis or retinitis, *Cryptococcus neoformans* meningitis and *Toxoplasma* encephalitis, are recommended to warrant long-term maintenance therapy [9]. For reducing VZV load in the CSF to reduce the risk of an IRIS including ARN, we may consider secondary prophylaxis or long-term maintenance therapy for patients who developed VZV meningitis before initiation of ART.

Acknowledgements

We are grateful to Drs Masayuki Saijo and Souichi Yamada from the Department of Virology 1, National Institute of Infectious Diseases, for analyzing gene sequences to detect mutations in thymidine kinase genes of VZV for resistance to acyclovir.

All authors meet the above ICMJE authorship criteria. T.H. had mainly treated the patient during hospitalization and drafted the article. Y.U. had mainly treated the patient after discharge as an outpatient and revised the article for important intellectual content. T.K. revised the article for important intellectual content, especially in the ophthalmic parts. T.N. made final approval of the version to be submitted.

T.N. has received honoraria for lectures from MSD. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

There are no conflicts of interest.

Tomohiro Hosoda[a], Yuki Uehara[a], Toshimitsu Kasuga[b] and Toshio Naito[a], *[a]Department of General Medicine, and [b]Department of Ophthalmology, Juntendo University Faculty of Medicine, Tokyo, Japan.*

Correspondence to Tomohiro Hosoda, Department of Infectious Disease, Kawasaki Municipal Kawasaki Hospital, 12-1 Shinkawa-dori, Kawasaki-ku, Kawasaki City, Kanagawa 210-0013, Japan.
Tel: +81 44 233 5521; fax: +81 44 245 9600; e-mail: ottotto723@gmail.com

Received: 20 October 2019; revised: 10 December 2019; accepted: 14 December 2019.

References

1. Muthiah MN, Michaelides M, Child CS, Mitchell SM. **Acute retinal necrosis: a national population-based study to assess the incidence, methods of diagnosis, treatment strategies and outcomes in the UK.** *Br J Ophthalmol* 2007; **91**:1452–1455.
2. Cochrane TF, Silvestri G, McDowell C, Foot B, McAvoy CE. **Acute retinal necrosis in the United Kingdom: results of a prospective surveillance study.** *Eye* 2012; **26**:370–377.
3. Müller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M. **Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis.** *Lancet Infect Dis* 2010; **10**:251–261.
4. Haddow LJ, Easterbrook PJ, Mosam A, Khanyile NG, Parboosing R, Moodley P, *et al*. **Defining immune reconstitution inflammatory syndrome: evaluation of expert opinion versus 2 case definitions in a South African cohort.** *Clin Infect Dis* 2009; **49**:1424–1432.
5. Suzutani T, Saijo M, Nagamine M, Ogasawara M, Azuma M. **Rapid phenotypic characterization method for herpes simplex virus and varicella-zoster virus thymidine kinases to screen for acyclovir-resistant viral infection.** *J Clin Microbiol* 2000; **38**:1839–1844.
6. Teo SY, Raha D, Warren D, Hassan A, Monteiro E. **Central nervous system-immune reconstitution inflammatory syndrome presenting as varicella zoster virus-mediated vasculitis causing stroke.** *Int J STD AIDS* 2014; **25**:683–685.
7. Newsome SD, Nath A. **Varicella-zoster virus vasculopathy and central nervous system immune reconstitution inflammatory syndrome with human immunodeficiency virus infection treated with steroids.** *J Neurovirol* 2009; **15**:288–291.
8. Clark BM, Krueger RG, Price P, French MA. **Compartmentalization of the immune response in varicella zoster virus immune restoration disease causing transverse myelitis.** *AIDS* 2004; **18**:1218–1221.
9. Centers for Disease Control and Prevention (CDC). National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America; 2019. https://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. [Accessed 4 October 2019].

DOI:10.1097/QAD.0000000000002477